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Re: NAS 0; Not Product Specific
Response to FDA Request/Comment: Other
Docket No. 2005D-0183: Comments on the "Draft Guidance for Industry: Antiviral Drug Development - Conducting Virology Studies and Submitting the Data to the Agency," Federal Register, Volume 70, No. 100, Pages 30127-30128, May 25, 2005

Dear Sir or Madam:

Reference is made to the notice, as published by the Food and Drug Administration in the Federal Register on May 25, 2005, to invite written comments on a new draft guidance for industry ("Draft Guidance for Industry: Antiviral Drug Development – Conducting Virology Studies and Submitting the Data to the Agency") (1). The purpose of this letter is to provide comments on this new draft guidance.

GlaxoSmithKline is a research-based pharmaceutical and biotechnology company. Our company is dedicated to the discovery, development, manufacture, and distribution of medicines and vaccines that enable people to lead longer, happier, healthier, and more productive lives. GlaxoSmithKline has a long history of productive research and development of products for the treatment of HIV, herpes simplex, hepatitis B, and other viral infections. In these efforts, we have worked constructively for over two decades with the Division of Antiviral Drug Products and other groups within FDA, with our first antiviral for herpes simplex approved in 1982 and our first antiretroviral approved in 1987. GlaxoSmithKline holds FDA-approved New Drug Applications for Retrovir® (zidovudine) products, Epivir® (lamivudine) products, Ziagen® (abacavir sulfate) products, Agenerase® (amprenavir) products, and Lexiva® (fosamprenavir calcium) Tablets for the treatment of HIV infection. In addition, we hold FDA-approved New Drug Applications for Epivir-HBV® (lamivudine) products for hepatitis B, Relenza® (zanamivir for inhalation) for influenza, and Valtrex® (valacyclovir hydrochloride) Caplets and Zovirax® (acyclovir) products for herpes simplex. Our virology and clinical development groups have been involved in virologic testing throughout the development of our approved antiviral products and maintain continued interest and expertise in these

areas. In addition, we have ongoing activities to develop new drug products for a variety of viral infections. In view of our longstanding work in this field and our substantial interest in the topics in this new draft guidance, we welcome this opportunity to provide comments for FDA's consideration.

In the following sections, we provide comments on the draft guidance. We have provided comments on each major section of the draft guidance. The focal point of each comment is identified by the line numbers in the draft guidance. We trust that this approach will facilitate your review and consideration of our comments.

Most of our comments regarding antiretroviral agents and HIV parallel those that we submitted to the docket in February 2005 on another recent draft guidance for industry on "Role of HIV Drug Resistance Testing in Antiretroviral Drug Development," November 2004 (2).

General Comments

We welcome this draft guidance, which emphasizes the importance of reporting nonclinical and clinical virology data to FDA in the development of new antiviral agents. This draft guidance specifically covers HIV, hepatitis B (HBV) and hepatitis C (HCV) viruses; however, we suggest that the principles of this draft guidance could also be applied for antiviral agents in development for the treatment of herpes simplex virus, poxviruses (noted in the draft guidance, **Lines 243-245**), varicella zoster, influenza, cytomegalovirus, human papillomavirus, and other viral infections. Although the available assays and model systems vary with the viral agent, assessments of mechanism, activity, cytotoxicity, and resistance during development are generally applicable.

However, the availability of *in vitro* model systems and assays for viral identification, activity, replication, and resistance varies among the various viral agents noted above. In our comments below, we have attempted to identify some of the challenges for applying to HBV and HCV the antiviral development principles applicable to HIV. As a guiding principle, we note that the availability of robust and validated model systems and assays will determine the extent of the data that can be submitted to FDA in support of the development of new antiviral agents. The requirements and details of such data should be discussed with the Division during the periodic meetings scheduled during the course of development of a new antiviral drug product.

- At this time, very limited FDA-approved HIV resistance assays are available for use by sponsors developing antiretroviral drugs. Assays for viral proteins and quantitative assays for viral DNA are even more limited for hepatitis B and C. Therefore, the draft guidance should explicitly address some of the key issues that invariably arise when a sponsor of an investigational antiviral drug utilizes an investigational assay, particularly one conducted by a contract testing laboratory. It would be helpful if FDA can offer suggested avenues (e.g., master file, letter to the IND/NDA), other than a device marketing application, through which proprietary assay data could be provided by the testing laboratory in support of an IND or NDA. Furthermore, it would be helpful if FDA can state that an NDA will not be judged deficient due to the absence of information on the performance characteristics of a given investigational assay. Also, labeling for prescription antivirals should state, in the DESCRIPTION OF CLINICAL STUDIES section, the identity of any investigational or approved assays used in adequate and well-controlled trials.

I. BACKGROUND (Pages 1-2, Lines 36-58

Lines 55-56: Please clarify the readiness of CDER to accept electronic IND submissions.

II. NONCLINICAL VIROLOGY REPORTS (Pages 2-10, Lines 59-418)

A. **Overview** (Pages 2-3, Lines 61-96)

Lines 87-93: The progression path suggested for conducting nonclinical virology studies is generally in line with that currently used for many antiviral development programs. As noted in the draft guidance, many of the nonclinical studies considered key for the development of HIV drugs translate into other viral areas. However, some studies that are relatively straightforward to perform with HIV are not possible with other viruses. Specifically, the draft guidance recommends "examining the *in vitro* selection of resistant viruses to the investigational drug, the phenotypic and genotypic characterization of the resistant viruses, and cross-resistance analyses before initiation of clinical studies in patients infected with the particular virus."

For HBV, there are no robust methods to identify resistance mutations that may emerge on clinical use, because there are no robust *in vitro* infection systems for this virus. Thus, many studies with specific drug-resistant HBV, which may be selected in clinical settings, can not occur until the potential drug is being evaluated in the clinic. Once mutations are identified, the sponsor has the ability to characterize these mutants in phenotypic and genotypic studies evaluating the degree of resistance, the impact of these

mutations on the physical characteristics of the virus (e.g., fitness), and cross-resistance to other antiviral agents. This progression pathway is, therefore, distinct from that acceptable for HIV drugs because of technical limitations of the field.

For HCV, a similar limitation may apply depending upon the molecular target. It is possible to select resistance mutations in some nonstructural HCV protein targets by passaging cells containing the viral replicon in the presence of potential antiviral drugs. No assay has been proven robust enough to select virus resistant to potential antivirals where the molecular target involves viral structural proteins. Thus, it may not always be possible to proactively determine genotypic resistance patterns or evaluate resistant virus prior to clinical studies.

B. **Recommended Components of Nonclinical Virology Reports** (Pages 3-10, Lines 97-418)

1. **Mechanism of Action** (Pages 3-4, Lines 99-141)

Lines 101-104: Although we recognize the need to determine to the best extent possible the mechanism of action (MOA) of a new drug prior to Phase 1, this may be more difficult for new drugs with a novel MOA or for new drugs for some viruses for which few antivirals currently exist. An example would be an antiviral interacting with an as-yet unidentified cellular protein necessary for virus replication. In addition, certain principle metabolites may not be identified until after clinical administration. Therefore, we recommend that the guidance be less stringent in terms of determining MOAs, particularly for metabolites, prior to Phase 1.

2. **Antiviral Activity** (Pages 4-6, Lines 142-246)

Lines 155-158: A critical point for translation of this draft guidance to development of antivirals for hepatitis B and C is found in the words "If possible" -- we suggest addition of this wording "if possible" to the various recommendations in the draft guidance for data relative to these viruses. The draft guidance recommends that sponsors "obtain antiviral activity data using primary human target cells. Because of viral genetic variation, the antiviral activity of the investigational drug should be examined for multiple clinical isolates and viral isolates representative of the virus population in clinical trials." The primary human target cell for HBV and HCV is the hepatocyte, which is of very limited availability considering that a human donor liver is required for each hepatocyte culture. Although infections of human hepatocyte cultures by these viruses are possible, these assays are not robust, with most clinical serum samples failing in infection assays. Thus, this proposal is not appropriate for drug development studies of

either HBV or HCV. Alternative assays frequently mimicking only portions of the viral replication scheme are well-suited to studies determining IC_{50} values for potential agents and for other studies defined in this section. The guidance describes this in **Lines 185-206.**

a. **Antiviral activity in vitro** (Pages 4-5, Lines 144-207)

b. **Antiviral activity in vitro in the presence of serum proteins** (Page 5, Lines 208-220)

Lines 214-218: The use of high concentrations of human serum in tissue culture can have toxic effects on the cells. Therefore, for HIV, we are inclined to include analyses where a series of dilutions of human serum (e.g., 5%, 10%, 20%, 40%) are employed and extrapolated to 100%.

Lines 218-219: We acknowledge the effects of alpha-1 acid glycoprotein relative to the protein-binding effects of HIV protease inhibitors, but we also routinely examine the protein-binding effects of human serum albumin at physiological concentrations.

c. **Inhibitory quotient** (Pages 5-6, Lines 221-233)

d. **Antiviral activity *in vivo*** (Page 6, Lines 234-246)

We acknowledge the utility of animal models in evaluating antiviral activity; however, translation of information from model systems with surrogate viruses (or even the actual target virus) is not simple. For example, for HBV resistance patterns selected in one system (i.e., the woodchuck infected with woodchuck hepatitis virus, WHV) may be quite distinct from those actually selected in humans. In addition, it is recognized that disease parameters in model systems may be quite distinct from those seen in humans infected with the same agent.

3. **Cytotoxicity/Therapeutic Index** (Pages 6-7, Lines 247-273)

4. ***In Vitro* Combination Activity Analysis** (Page 7, Lines 274-290)

5. **Resistance** (Pages 7-10, Lines 291-418)

a. **Selection of resistant virus *in vitro*** (Pages 7-8, Lines 293-337)

Lines 325-336: Since the selection of resistant variants is difficult and time consuming, the guidance should specify exactly what the Division expects the sponsor to produce for viruses with *in vitro* replication models. Repeating selection experiments several times is not necessary; we recommend that the draft guidance state that the sponsor is expected to conduct *in vitro* experiments to endeavor to select drug-resistant variants under two conditions, i.e., high selective pressure and low selective pressure. Drug susceptibility should be determined both with viruses selected and with recombinant viruses containing selected mutations.

Also, please see inserted comments under Section III.A. (**Lines 87-93**). For HBV, it is not currently possible to accurately predict resistance in clinical studies from *in vitro* selection of resistance mutations. For HCV, it is only possible to select resistance for antivirals with nonstructural molecular targets represented in the replicon assay. Although an infection system has been recently characterized (3) that may prove useful for selecting drug-resistant HCV with mutations in the structural genes, this system is unproven. This infection system was initially described for a specific construct of genotype 2a, but it is not clear if this infection system will translate to other genotypes. HCV can be passaged in culture with this system; however, it has not been proven that this system is robust enough to use for the selection of drug-resistant HCV virus isolates.

b. **Genotypic analysis** (Pages 8-9, Lines 338-359)

c. **Phenotypic analysis** (Page 9, Lines 360-396)

Lines 385-393: To our knowledge, the Center for Biologics Evaluation and Research in FDA has permitted marketing of only two *in vitro* HIV drug resistance genotype assays (i.e., TRUGENE® HIV-1 Genotyping Kit and OpenGene® DNA Sequencing System [from Visible Genetics, Inc.] as of September 26, 2001 and ViroSeq™ HIV-1 Genotyping System [from Applied Biosystems/Celera Diagnostics] as of January 15, 2003). FDA's authorization for marketing of these two genotyping assays was in accordance with CBER's guidance governing *in vitro* HIV drug resistance genotype assays (4).

We are not aware that any of the various *in vitro* HIV phenotypic resistance assays (e.g., PhenoSense™ by ViroLogic, Antivirogram® by Virco) or other *in vitro* HIV genotypic resistance assays (e.g., GeneSeq™ by ViroLogic) have been reviewed by FDA and authorized for marketing. No phenotypic assays are approved, and only one tropism assay (PhenoSense™ Entry Assay by ViroLogic) is in investigational use, for assessment of whether an HIV-1 isolate utilizes the CCR5 or CXCR4 chemokine co-receptor.

The concepts proposed for HIV translate to HBV and HCV. We agree that a key commitment of the sponsor should be to evaluate resistance emerging in studies with investigational agents for HBV and HCV as well as HIV. The assays are quite distinct,

but the need crosses all areas for these assays to be heavily validated. While we know of no FDA-approved assays for evaluating genotypic resistance to antiviral agents for HBV or HCV, there are a number of commercially available assays that have been used by many groups in evaluating genotypic resistance for these viruses. For both HBV and HCV, these assays include standard sequence analyses to detect mutations at numerous sites in the viral genome. For HBV, where specific sites in the viral polymerase have been linked to resistance with selected antiviral agents, a variety of site-specific assays have been developed and used for routine evaluations of genotypic resistance in clinical trials (e.g., INNO-LiPA HBV DR™ and INNO-LiPA HBV DR II™ by Innogenetics). There are no currently available phenotypic assays for HBV or HCV. ViroLogic, and perhaps Virco, are developing replicon-based resistance assays for evaluating resistance in HCV NS5b polymerase and the NS3 protease, but these assays are in relatively early stages. It is likely that the sponsor's laboratory support for phenotypic assays will continue to be key when agents for HBV and HCV are developed.

In recognition of this situation and since the draft guidance encourages use of genotypic and phenotypic assays of viral resistance, the draft guidance should explicitly address some of the key issues that invariably arise when a sponsor of an investigational antiviral drug utilizes an unapproved resistance assay, including the following issues:

- Usually, for an unapproved assay, there is no regulatory application at FDA containing data and other information on the performance characteristics of the assay. Such information is usually not available to sponsors who may apply the assay in clinical studies. Although we recognize FDA's need to evaluate the quality of the assay in the context of review of a sponsor's New Drug Application (NDA), the sponsor is unable to ensure that such proprietary assay data are provided by the testing laboratory. It would be helpful if FDA can state that an NDA will not be judged deficient due to the absence of information on the performance characteristics of an unapproved assay of antiviral drug resistance and if FDA could offer suggested avenues (e.g., master file, letter to IND/NDA), other than a device marketing application, through which proprietary assay data could be provided by the testing laboratory in support of an NDA.
- For *in vitro* resistance assays of genotype, when data on assay performance is available, it would be helpful if FDA can confirm the expectation that the sponsor (or contract testing laboratory) should provide information on assay performance, consistent with Sections III.B-D in the guidance of August 2001 (4).
- Labeling of prescription drug products should state, in the DESCRIPTION OF CLINICAL STUDIES section, the identity of any investigational or approved *in vitro* viral resistance assay used in adequate and well controlled trials. Methodology and performance characteristics of the assay are appropriate for inclusion via citation to a

REFERENCES section of labeling (as has been routine for many years for methods of assessing bacterial susceptibility to antibacterial drug products).

d. **Cross-resistance** (Pages 9-10, Lines 397-418)

Lines 412-415: The guidance asks for phenotyping of "multiple clinical isolates." For a new investigational antiretroviral, we routinely evaluate at least 20 laboratory strains and at least 50 recombinant viruses derived from contemporary plasma of HIV-infected patients – we trust that such numbers of isolates are reasonable and consistent with FDA's intent to provide some flexibility for scientists to select a reasonable collection of laboratory and clinical isolates. For other viruses, such numbers of isolates may not be reasonably available.

We agree that cross resistance assays are important for HBV and HCV virus profiles. However, technical considerations again require distinct assay plans from those used with development of HIV agents. As discussed in previous sections, it is not currently possible to perform routine phenotyping assays with multiple clinical isolates for HBV and HCV antiviral drug development because there is no robust infection system available using clinical isolates. Therefore, cross-resistance assays for HBV and HCV will require the generation of selected mutations onto common backbones and evaluation in defined recombinant systems. For HBV and HCV, these systems are likely to involve only selected components of the viral replication cycle.

I. **PROPOSAL FOR MONITORING RESISTANCE DEVELOPMENT** (Pages 10-11, Lines 419-481)

Lines 430-435: See comments above for **Lines 385-393**.

Lines 454-467: Even for virus for which such assays are available, requiring baseline genotype and phenotype on all patients will have very limited scientific yield, be impractical, and be cost prohibitive in many clinical studies. We note that our current discounted HIV assay costs are $500 per specimen for a genotype test and $950 per specimen for a phenotype test. The yield of scientific information will be very limited in some situations, such as a controlled clinical trial in therapy-naïve HIV patients in the US, where the prevalence of drug-resistant virus at baseline is still less than 10-15% in most areas. For most other viruses, the prevalence of drug-resistance at baseline would be negligible. Requiring baseline genotype and phenotype will be impractical and cost prohibitive in many clinical studies, including certain large clinical studies, certain studies conducted in geographic settings with limited or no laboratory resources, and certain studies sponsored by governmental or other collaborative clinical trial groups.

Particularly for a new investigational antiretroviral for first-line therapy, our recommendation would be to collect and store baseline samples for all patients, but only assay baseline genotype and phenotype for patients with subsequent virologic failure. Baseline genotype and phenotype could also be determined on an additional representative subset of the patients if appropriate to the objectives of the study. If baseline testing is desired on all study patients, we suggest that it be limited to genotypic testing only for antiretroviral RTIs and PIs, as this is less costly and more likely to be provide useful data. On the other hand, for a new antiretroviral product seeking explicit labeling for treatment-resistant virus, genotype and phenotype analyses of samples from baseline and on-treatment are pertinent throughout development. Overall, we suggest that the extent and type of resistance testing be discussed and agreed upon with the Division up front and be commensurate with the scientific value of the resulting data relative to study intent and nature of the drug target versus the effort and cost of such testing.

For HBV and HCV, we agree that baseline and post-treatment genotypic analyses will be key in monitoring genotypic resistance development. Given the lack of the ability to predict genotypic resistance sites for HBV prior to clinical study in many instances, performing genotypic analyses on samples exhibiting virologic breakthrough with comparative analyses of baseline samples may be the only method available to identify mutations selected in resistant viruses. We recommend that the extent and type of resistance monitoring and analyses be discussed and agreed upon with the Division in advance.

Lines 474-479: We would like to point out that the obligation of the sponsor to submit viral resistance data is directly related to the nature of resistance statements sought by the sponsor in draft labeling in the future NDA. The more extensive and detailed the statements sought in draft labeling, the more evidence need be provided by the sponsor.

GSK has submitted virology data in the past and is very willing to do so in future applications, in accordance with statements sought in draft labeling. Importantly, we take this opportunity to remind FDA that it is essential that we fully agree on the format and content of such data at the pre-NDA meeting (per 21 CFR 312.47) in order to ensure that the sponsor can provide all information and analyses needed for FDA's review in the original NDA submission. The data tables provided to FDA and subsequent information included in labeling should be consistent with the objectives of the drug development program. We recommend that the Division remain open to a variety of text descriptions as well as tabular displays, and we appreciate the illustrative displays provided in the appendices if this draft guidance.

II. VIROLOGY STUDY REPORTS (Pages 11-12, Lines 482-495)

General: Please indicate where such reports should be provided for an NDA in CTD format. Per our experience with the Division, we have been instructed to include resistance assay information, as well as clinical virology reports, in Module 5, Section 5.3.5.4 "Other Studies" under a specific heading for "Antiviral Reports."

APPENDIX 1: TEMPLATE FOR SUBMITTING HIV RESISTANCE DATA

Lines 532-539: Please correct the typographical errors of "HBV" to "HIV."

III. Genotypic Data

Line 723: According to a recent publication (5), the prevalence of non-clade B viruses is < 2% in blood donors in the US. We typically test activity against non-clade B viruses *in vitro*, but not for clinical isolates.

IV. Protease Cleavage Sites

Lines 582-590: Regarding the protease cleavage sites for PIs, it has been accepted for several years that the NC/p1 and p1/p6 gag cleavage sites are the most critical for polyprotein processing and are the rate-limiting sites where the key mutations arise. We see no rationale for including the p2/NC cleavage site; for us to do so would require further assay development.

IX. Co-Receptor Usage

Lines 659-660: Evaluation of co-receptor tropism would be pertinent only for entry inhibitors that selectively target either R5- or X4-tropic virus. Other entry inhibitors (e.g., enfuvirtide) are unlikely to have greater potential to select for virus of a particular tropism than drugs targeting other viral genes (e.g., RT, PRO, INT).

Requiring baseline tropism testing on all patients is likely to have limited scientific yield and be cost prohibitive in many clinical studies, as noted in **Lines 454-467** for resistance testing. Epidemiologic studies presented to date (6, 7, 8) have shown the prevalence of X4-utilizing virus (i.e., R5X4) at baseline to be approximately 15%, with less than 4% being X4 only. For your information, we note that our current discounted assay cost is >$600 per tropism test.

It may not be possible to assay R5 and/or X4 (in terms of "relative light units" or RLU) at the end of the study as the viral load may be too low. The lower validated limit of the tropism assay (PhenoSense Entry Assay) is 1000 c/mL. We note that the draft guidance requests R5 and X4 assay values at failure/end of study as well as at baseline – the RLU values have no correlation with the quantity of these quasi-species and, therefore, their inclusion is of questionable value. In addition, the draft guidance does not indicate that clonal analysis data and phylogenetic data should be included; however, in our experience, these data have been requested by the Division.

APPENDIX 2: TEMPLATE FOR SUBMITTING HBV RESISTANCE DATA

For the development of antivirals impacting both HBV as well as HCV, we would highlight the point made above (**Lines 474-497**) that the obligation of the sponsor to submit viral resistance data is directly related to the nature of resistance statements sought by the sponsor in draft labeling in the future NDA. The more extensive and detailed the statements sought in draft labeling, the more evidence need be provided by the sponsor.

II. Endpoint Data

Lines 710-722: We would recommend that all endpoint data for viral level have linked information about the assay used. Although highly undesirable, it may be necessary to change assays in long-term studies during the course of the trial and not possible to re-evaluate markers with new assays in old samples. As such, it is key that all data be identified as to which assay was used.

III. Genotypic Data

Lines 724-725: Please clarify that genotypic changes refer to changes from actual baseline data acquired in the same patient. This is important since some HIV studies identify treatment-emergent mutation patterns based on prototypic baseline sequences and not through comparison to the same patient's baseline sample.

Lines 734-738: Please note that this presentation may only be optimal if short segments of the genome are evaluated. If large sections of the genome are sequenced, or a large number of variant or mutant sequences are detected, then alternative presentations may be more appropriate.

It is understood that the time points are presented as an example. For many commitments, longer-term follow-up may also be key.

IV. Phenotypic Data

As stated previously (see **Lines 385-393**), phenotypic data for HBV agents should not be defined according to HIV standards as the technical limitations require different approaches. Baseline phenotype data are limited to a prototypic virus assay. Subsequent assays evaluating selected mutants are limited to recombinant assays with selected mutants put onto the backbone of a prototypic virus.

Lines 764-773: The sample table would need modification, as it implies that phenotypic data are available that are directly relevant for each clinical isolate. These data are not available as assays are not available to support this. The "Baseline" row should be "Reference Strain." The "Endpoint" row should refer to a specific mutation pattern being evaluated. Thus, for each study, there would be only a single reference strain (for example, data from a HepG2, 2.2.15 cell line with a defined 'wild type' construct) and multiple mutation patterns would have data presented.

APPENDIX 3: TEMPLATE FOR SUBMITTING HCV RESISTANCE DATA

For the development of antivirals impacting both HCV as well as HBV, we would highlight the point made above (**Lines 474-497**) that the obligation of the sponsor to submit viral resistance data is directly related to the nature of resistance statements sought by the sponsor in draft labeling in the future NDA. The more extensive and detailed the statements sought in draft labeling, the more evidence need be provided by the sponsor.

Lines 788-789: Please note that patients with sustained virologic response may not have sufficient levels of virus for genotype/phenotype.

Lines 800-804: Please correct the typographical error of "HBV" to "HCV."

II. Endpoint Data

Lines 822-833: We would recommend that all endpoint data for viral level have linked information about the assay used. Although highly undesirable, it may be necessary to change assays in long-term studies during the course of the trial and not possible to re-evaluate markers with new assays in old samples. As such, it is key that all data be identified as to which assay was used.

Lines 834-835: Regarding the requirement for an HCV viral load assay with a lower limit of quantification less than 100 copies/mL, it would be preferred if this limit were expressed in international units (IU)/mL, as these are a standardized unit of measure across all HCV viral load assays whereas copies/mL are not. Furthermore, we note that the only HCV viral load assay approved by FDA, the Versant™ HCV RNA 3.0 Assay from Bayer Healthcare, LLC, does not meet this requirement.

III. Genotypic Data

Lines 837-838: Please clarify that genotypic changes refer to changes from actual baseline data acquired in the same patient. This is important since some HIV studies identify treatment-emergent mutation patterns based on prototypic baseline sequences and not through comparison to the same patient's baseline sample.

Lines 846-851: Please note that this presentation may only be optimal if short segments of the genome are evaluated. If large sections of the genome are sequenced, or a large number of variant or mutant sequences are detected, then alternative presentations may be more appropriate.

For HCV analyses, it is possible that quasi-species may be evaluated. Thus, it needs be recognized that this presentation may be modified to include the presentation of multiple clonal analyses from a single sample.

It is understood that the time points are presented as an example. For many commitments, longer-term follow-up may also be key.

IV. Phenotypic Data

As with HBV, it is not currently possible to perform routine phenotypic analyses on HCV clinical isolates as no such phenotypic assay is available. Thus, these data are likely to be generated with selected mutants on a few prototypic backbone viral constructs.

Lines 880-889: The sample table again would need modification as it implies that phenotypic data are available that are directly relevant for each clinical isolate. These data are not available as assays are not available to support this. The "Baseline" row should be "Reference Strain" or "Replicon." The row labeled "Endpoint" for HCV should expand -- It may refer to a specific mutation pattern being evaluated or to a portion of which clinical isolate has been inserted into a prototypic backbone for evaluation. Thus, initial data for each study would include only a single reference strain (for example, data from the genotype 1b replicon cell with a defined 'wild type' construct). Multiple mutation patterns selected *in vitro* or identified through genotypic

analysis of clinical isolates would have data presented as endpoint data. For selected samples, it may be possible to recombine into replicons large portions of clinical isolate HCV genomes to better mimic the clinical isolate viral backbone.

Again, we thank you for this opportunity to provide comments on this important topic. This submission is provided in paper and electronic format according to the instructions provided at

http://www.accessdata.fda.gov/scripts/oc/dockets/comments/commentdocket.cfm?AGENCY=FDA.

Please contact Susan L. Watts at (919)-483-5540 or David M. Cocchetto at (919)-483-5127 for any matters regarding this submission. If you wish clarification or further discussion of our comments, we would be pleased to schedule a teleconference or meeting in follow-up. Thank you.

Sincerely,

Susan L. Watts

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Associate Director, Antiviral/Antibacterial
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David M. Cocchetto

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